III, t-PA and procoagulant levels several months later. The problem with this approach is that hundreds of women per 10,000 users will show significant alterations in the hemostatic balance, but in only about 20 of them each year will a thromboembolic event develop. It would appear that the cost/benefit ratio would not favor such an expensive approach, which is likely to have a high false-positive index.

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It Could Be an Important First Step

AT ITS MEETING in June of this year the House of Delegates of the American Medical Association (AMA) adopted report MM of the Board of Trustees. This could prove to be an important action by the AMA. The report is the result of a careful study by the Council on Medical Service, the Council on Legislation and the Board of Trustees. It is a thoughtful proposal for financing (or refinancing) the health care of the elderly in this nation. It addresses a number of problems that must be dealt with realistically if the Medicare program is not to face almost certain fiscal and perhaps even political disaster in the years ahead.

The AMA proposal would eliminate the current Medicare program but honor the commitments already made to the elderly. To this writer the specifics of the plan are not as important as are some of the principles it embodies. It restores the original purpose of Medicare, which was to provide access to affordable high quality health care for the elderly, and to this end it would remove care for the disabled (unless elderly) and the care of end stage renal disease (ESRD) from the program except for the elderly. These needs would then be financed from some other source.

Another basic concept of the AMA proposal is that Medicare be self-funded, but in a new way. At present about four workers are taxed to support the health care of one Medicare recipient. By the middle of the next century demographic change will reduce this to only two workers, likely to be a politically unacceptable arrangement. And it has been estimated that the present program will be 1 trillion dollars in debt by the year 2010, likely to be an economically unacceptable arrangement. The AMA proposal wisely envisions a new approach. Over time, that is before the middle of the next century, the present intergenerational transfer of resources from earners to Medicare beneficiaries will be replaced by a program prefunded by the potential beneficiaries themselves through tax contributions during their own working years. This would be augmented by voluntary health individual retirement accounts (HIRAs) which would be tax free if used to cover supplemental health care expenses. The proposal would also create a new semiautonomous federal agency to administer the program. This would be somewhat on the model of the Federal Reserve Board to give it a modicum of political independence. Other provisions would take advantage of the resources of the private sector to provide the health care, and would require some reasonable fiscal participation by the beneficiaries based on their ability to pay as determined by their annual incomes. Conspicuously absent from the proposal, which otherwise seems quite comprehensive and well thought out, is any mention of utilization review or cost control. It would seem that these will be as important in any new program as they have been found to be in the program as we know it now. But the report makes no claim to be complete or final. It is only being presented at this time with the hope that it will stimulate discussion and debate, and indeed it should.

The AMA is surely to be commended for developing this imaginative and innovative proposal. It seems in many ways to be right on target. It can be viewed as affirmative action in behalf of patients and the public. One can hope that discussions with other interested parties will develop, and that in time all those with interests at stake will become involved. One can also hope that as this occurs, and some sort of agreement or consensus is reached, an effective coalition of various groups and parties at interest will come into being and thus provide the energy and resources necessary to bring about the change that by then they all will have recognized as needed and desirable. Experience would suggest that it is unlikely that the physicians of America and the AMA can do all this alone, but the proposal adopted by the House of Delegates could be an important first step. The AMA plans to encourage wide discussion of the proposal and the problems it seeks to solve, and let us all hope that this occurs.

MSMW

Pheochromocytoma

THERE is no more important and treacherous cause of hypertension to recognize and treat appropriately than pheochromocytoma since the tumor can be successfully removed in 90% of patients. If unrecognized, it will usually cause a catastrophic cardiovascular event or death. Therefore, even though pheochromocytoma is a rare cause of hypertension (probably occurring in less than 0.1% of the population with diastolic hypertension), it is extremely desirable to repeatedly expose and sensitize clinicians to the vagaries of this most exciting and fascinating "pharmacologic bomb"—a tumor whose clinical expression, often dramatic and explosive, has rightly earned it the title of "the Great Mimic."

The clinicopathologic conference in this issue is a highly valuable exercise (as were two cases of pheochromocytoma recently reported as clinicopathologic exercises in the *New England Journal of Medicine,* Case 9-1985 [1985; 312: 568-575] and Case 6-1986 [1986; 314:431-439]). Dr Rutledge's admirable discussion of the differential diagnosis and

his approach in determining the correct cause of this patient's hypertension are most instructive.

One cannot emphasize too often the simple fact that the diagnosis of pheochromocytoma has been frequently missed because it was never considered.[1] We have found that a detailed history and physical examination can be of great value in deciding which patients with sustained or paroxysmal hypertension should be screened for pheochromocytoma since approximately 95% of patients are symptomatic. A very small percentage of pheochromocytomas cause manifestations without hypertension. It is noteworthy that tumors in patients with familial pheochromocytoma not infrequently remain relatively silent and cause few if any signs or symptoms of excess circulating catecholamines.[2(p37)] Indications for screening patients for pheochromocytoma are given in Table 1.

With regard to the present case report, it was not indicated whether the patient gave a history of recurrent headaches, palpitations or generalized sweating during the year he was known to have hypertension. Since about 95% of patients with pheochromocytoma have one or a combination of these manifestations, the absence of them is good evidence against the diagnosis of pheochromocytoma. Headache, the most common symptom, occurs abruptly and may be very severe and throbbing during a paroxysm of hypertension; it subsides as the blood pressure returns toward normal. It is often accompanied by nausea and vomiting. In patients with sustained hypertension, the headaches may be severe, but usually the intensity is moderate to mild and indistinguishable from tension headache or that occasionally experienced by some patients with essential hypertension. About two thirds of patients perspire excessively. Sweating (sometimes drenching) is generalized and most profuse during or immediately following a paroxysmal attack of hypertension. Palpitations, a sense of "pounding" in the chest, is the third most common symptom and is usually accompanied by tachycardia, although reflex bradycardia may be induced by the increased blood pressure.

TABLE 1.—*Indications for Screening Patients for Pheochromocytoma*

Hypertension (sustained or paroxysmal) with the following
Symptoms and signs*
Group 3 or 4 retinopathy of unknown cause
Weight loss
Hyperglycemia
Hypermetabolism without hyperthyroidism
Cardiomyopathy
Orthostatic hypotension (without antihypertensive therapy)
Persons with pronounced hyperlability of blood pressure
Recurrent attacks of symptoms and signs of pheochromocytoma, even if hypertension not found
Severe pressor response during or induced by the following
Anesthesia induction
Intubation
Surgery
Angiography
Parturition
Antihypertensive therapy
Factors listed under "Clinical Presentation"*
Unexplained circulatory shock
During anesthesia
During pregnancy, delivery or in puerperium
During an operation or postoperatively
Following administration of phenothiazine drugs
Family history of pheochromocytoma, especially in the presence of hypertension (also screen siblings and children)
Persons with hypertension with disease or complications sometimes associated with pheochromocytoma†
Apparent preeclampsia or eclampsia with a hyperlabile blood pressure or severe hypertension
Transient abnormal electrocardiogram during hypertensive episodes
X-ray evidence of a suprarenal mass

*See Tables 1 and 2, Manger et al,[2] (or see Tables 4.1 and 4.3, Manger and Gifford[3]).
†See Table 2, Manger et al.[2]

Hyperthermia has been occasionally noted in patients with pheochromocytoma—apparently the result of vasoconstriction and the hypermetabolism caused by excess circulating catecholamines.[3(p103)] As suggested by Dr Rutledge, the hypothermia in the patient reported may have been related to impaired thermoregulation due to the hypertensive encephalopathy. The latter was probably responsible for the patient's severe headache on the day before admission.

The coexistence of hypertrophic cardiomyopathy in a patient with pheochromocytoma is intriguing but has only rarely been previously mentioned[4(p1310)] or reported.[5] Cardiomyopathy disappeared within five months after removal of the tumor. It is interesting to speculate that a trophic effect of excess circulating catecholamines on the myocardium may have been responsible for the hypertrophic cardiomyopathy and hemodynamic dysfunction; however, the extent to which the hemodynamic effects and hypertension per se contributed to the myocardial hypertrophy cannot be assessed. In patients with a systolic murmur and cardiomegaly, the echocardiogram can establish the diagnosis of hypertrophic cardiomyopathy and prompt a physician to avoid using inappropriate drugs, such as inotropic agents, nitrates and diuretics. Although I and my colleague, Ray Gifford, Jr, MD, agree with most of the general remarks made by Dr Rutledge about pheochromocytoma, there are several points of disagreement that deserve comment. We have found no good correlation between the amount of catecholamines secreted by pheochromocytomas and the clinical and laboratory manifestations; however, the rare occurrence of hypertension alternating with hypotension has been reported in patients with predominantly epinephrine-secreting tumors. This "manic-depressive" behavior of the blood pressure should immediately suggest pheochromocytoma.[3(p98)] We are unaware of any tumors secreting only dopamine and, even in pheochromocytomas that secrete dopamine in addition to other catecholamines, our patients have been hypertensive rather than normotensive or hypotensive. The presence of diarrhea would suggest the secretion of vasoactive intestinal polypeptide by the tumor since excess circulating catecholamines inhibit peristalsis and cause constipation, sometimes severe. Rarely, diarrhea may result from the secretions (prostaglandin, serotonin, calcitonin) of a coexisting medullary thyroid carcinoma. We have not encountered hypoglycemia in patients with pheochromocytoma. This has been rarely observed only in the immediate postoperative course after tumor removal.[2(pp57,58)]

Dr Rutledge mentions that "hypotension is commonly noted with pheochromocytoma." It should be reemphasized that either paroxysmal or sustained hypertension is present in almost all patients with pheochromocytoma. Only very rarely is hypotension a manifestation. It is true, however, that "or-

thostatic hypotension" is observed in some patients with sustained hypertension due to pheochromocytoma. This phenomenon is not, however, observed in patients who are normotensive and who have only paroxysms of hypertension. Orthostatic hypotension may result from a reduced blood volume, a decreased sympathetic reflex or a desensitization of adrenergic receptors due to excess circulating catecholamines.[2(p54)]

In the case reported, it is interesting that verapamil administration resulted in hypotension, since nifedipine (also a calcium-channel blocker) suppressed clinical symptoms and catecholamine levels in another patient with pheochromocytoma.[5] It is not surprising that intravenous administration of metoprolol caused a pronounced elevation of blood pressure since β-blockade alone, without first creating an α-blockade, may induce a hypertensive crisis in patients with pheochromocytoma.[2(p45)]

Only a small percentage of patients suspected of having pheochromocytoma actually have the disease. Even at medical centers where a large number of patients were referred for evaluation and screening for pheochromocytoma, the incidence is usually reported to be less than 1%.[3(p4)]

A preoperative diagnosis of pheochromocytoma demands the showing of elevated levels of plasma or urinary catecholamines or their metabolites. Without chemical or radiologic evidence of a tumor, an exploratory operation is not justifiable. In patients with sustained hypertension due to pheochromocytoma, levels of plasma and urinary catecholamines or their metabolites are invariably elevated. If the concentrations of plasma catecholamines are only slightly or moderately elevated ($< 2{,}000$ pg per ml), the ability of clonidine to suppress the sympathetic nervous system and reduce plasma norepinephrine to normal levels in patients with neurogenic hypertension but not in those with pheochromocytoma confers diagnostic specificity.[6]

In a very small percentage of patients with pheochromocytomas that cause paroxysmal hypertension, secretion of catecholamines occurs only periodically and the plasma and urinary catecholamines and their metabolites may be normal when the blood pressure is relatively normal. In these patients it is imperative either to obtain blood during a hypertensive period (spontaneous or provoked) or to collect urine shortly following a hypertensive episode because occasionally a preoperative diagnosis can only be made in this way. Our experience and that of our colleagues indicate that plasma catecholamine determination is an extremely reliable method of diagnosing pheochromocytoma—false-negative results are exceedingly rare.[7]

The measurement of total metanephrine (metanephrine plus normetanephrine) in a 24-hour urine specimen seems to be a most reliable method of screening because more than 95% of patients with pheochromocytoma have elevated levels. The quantitation of metanephrines is technically easier and fewer drugs interfere with this assay than with assays of catecholamines and vanillylmandelic acid.[2(p41)] A complete 24-hour urine collection is important for proper interpretation of results; severe stress should be avoided since stress may significantly elevate catecholamines and their metabolites. Abnormal elevations of catecholamines and their metabolites can be detected in "spot" (random) specimens of urine by showing an increase in the ratio of these substances to creatinine; however, we prefer a 24-hour collection. Rigid dietary restriction is unnecessary with current methods.

If a significant fraction of urinary catecholamines is epinephrine or its metabolite (metanephrine), or if a plasma epinephrine level is elevated, it is highly probable that the pheochromocytoma is in the adrenal area, although this is not invariably so. Some investigators have emphasized the value of determining both epinephrine and norepinephrine levels in plasma and urine when familial pheochromocytoma is suspected since these tumors are almost always located in the adrenal glands and usually secrete epinephrine.[2(p38)] It should also be emphasized that appropriate screening for medullary thyroid carcinoma and hyperparathyroidism be done in all patients following removal of a pheochromocytoma to exclude multiple endocrine neoplasia syndromes.

Computed tomographic (CT) scanning can identify 95% of pheochromocytomas. It is extremely accurate in showing lesions 1 cm or greater in the adrenals and 2 cm or greater in extraadrenal locations of the abdomen. When a pheochromocytoma cannot be located by CT scan of the abdomen, chest and neck, scintigraphy with ^{131}I-metaiodobenzyl guanidine—a radiopharmaceutical agent with a propensity to accumulate in pheochromocytomas—may be helpful in localizing the tumor and providing evidence of function, although results are false-negative in at least 15% of cases; only a relatively small percent of malignant pheochromocytomas may be visualized with this contrast agent.[2(p48)] If these methods fail to show the tumor site, then vena caval blood sampling may be helpful in localization.

In the past few years we have not needed angiography to localize pheochromocytomas. Most recently it has been noted that magnetic resonance imaging, although not providing the resolution of a CT scan, may be very helpful in confirming the presence of a pheochromocytoma.[8] The behavior of signal intensity observed on a magnetic resonance imaging scan appears to be characteristic of pheochromocytoma and certain other endocrine tumors.

The key to diagnosis is to think of pheochromocytoma in any patient with sustained or paroxysmal hypertension; all patients with any manifestation suggesting the presence of this tumor should be screened when the cause of hypertension is uncertain.

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